

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00, 31/56	A1	(11) International Publication Number: WO 95/31964 (43) International Publication Date: 30 November 1995 (30.11.95)
(21) International Application Number: PCT/EP95/01913 (22) International Filing Date: 19 May 1995 (19.05.95) (30) Priority Data: 9410222.5 21 May 1994 (21.05.94) GB (71) Applicant (for all designated States except US): GLAXO AUSTRALIA PTY. LIMITED [AU/AU]; 1061 Mountain Highway, Boronia, VIC 3155 (AU). (72) Inventors; and (75) Inventors/Applicants (for US only): TAINSH, David, Alexander [GB/GB]; Glaxo Research and Development Limited, Park Road, Ware, Hertfordshire SG12 0DP (GB). ILOTT, Trevor, Leslie [GB/GB]; Glaxo Research and Development Limited, Park Road, Ware, Hertfordshire SG12 0DP (GB). SNELL, Dorothy, Jill [AU/AU]; Glaxo Australia Pty. Limited, 1061 Mountain Highway, Boronia, VIC 3155 (AU). LAM, Li, Fong [AU/AU]; Glaxo Australia Pty. Limited, 1061 Mountain Highway, Boronia, VIC 3155 (AU). (74) Agents: DAWSON, Hugh, B. et al; Glaxo Wellcome plc, Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: FLUTICASONE PROPIONATE FORMULATIONS		
(57) Abstract The invention relates to formulations of use for the administration of medicaments by inhalation. In particular, the invention relates to a formulation which comprises fluticasone propionate substantially all having a particle size of less than 12 microns, one or more surfactants, one or more buffer agents and water. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of a formulation as defined is described also.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

FLUTICASONE PROPIONATE FORMULATIONS

5 This invention relates to improvements in or relating to pharmaceutical compositions comprising a fluticasone ester. In particular the invention relates to novel formulations of use in the administration of fluticasone propionate by inhalation.

10 Fluticasone propionate is the approved name for S-fluoromethyl 6a, 9a-difluoro-11b-hydroxy-16a-methyl-17a-propionyloxy-3-oxandrosta-1,4-diene 17b carbo-
thioate, a corticosteroid known to exhibit topical antiinflammatory activity and described and claimed in GB 2088877. In the treatment of asthmatic conditions it has been found to be effective to administer fluticasone propionate in the form of dry powders or aerosols containing small particles of the medicament,
15 conventionally prepared by micronisation. Conventionally, fluticasone propionate aerosols have been administered by means of metered dose inhalers, which are designed to deliver a fixed unit dosage of medicament per actuation or "puff". However, some patients, in particular children and the elderly, have difficulty in co-ordinating actuation of a metered dose inhaler with
20 inhalation, and are therefore unable to use this mode of administration effectively. Furthermore, a proportion of patients find inhalation of dry powders difficult or unpleasant. There is therefore a demand for a pharmaceutical formulation containing fluticasone propionate in a form suitable for nebulisation.

25 The present invention accordingly provides, in a first aspect, a formulation suitable for nebulisation comprising:-

- (a) Fluticasone propionate, substantially all having a particle size of less than 12 microns;
- 30 (b) one or more surfactants;
- (c) one or more buffer agents; and
- (d) water.

35 Fluticasone propionate may be prepared by methods known in the art, for example, as disclosed in GB 2088877. It will be appreciated that solvates of fluticasone propionate can be prepared and, accordingly, the present invention extends to formulations comprising physiologically acceptable solvates of fluticasone propionate. The particle size of the crystalline material may be

reduced by conventional methods, for example, by micronisation, and should be such as to permit inhalation of substantially all the medicament into the lungs upon administration of the nebulised formulation. Suitably the particle size will be in the range of 0.5 to 12 microns, such as 1 to 6 microns.

5

For introduction of the fluticasone propionate into the lungs, the droplet size of the nebulised formulation is an important parameter. Droplet size depends to some extent on the type of nebuliser used, whether a facemask or a mouthpiece is used and the pressure or flow rate of the compressed gas, as well as on the physical properties of the formulation for nebulisation. The nebulised formulation will be heterodisperse, i.e. droplets will cover a range of sizes. Typically, mean droplet size will be in the range of 0.5 to 15 microns, preferably 0.5 to 10 microns, more preferably less than 5 microns.

10 The formulation according to the invention desirably contains 0.5 to 10% w/w, preferably 1 to 9% w/w especially 1.5 to 6.5% w/w, of fluticasone propionate relative to the total weight of the solid ingredients of the formulation.

20 The surfactants used in the formulations of the present invention must be physiologically acceptable upon administration by inhalation. Within this category are included surfactants such as sorbitan trioleate (Span^R85), sorbitan mono-oleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan mono-oleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, glyceryl mono-oleate, polyethylene glycol 400 and glyceryl monolaurate.

25 Particularly preferred surfactants of use in the formulations of the present invention are sorbitan monolaurate and polyoxyethylene (20) sorbitan monolaurate (also known as polysorbate 20).

30 Suitably the formulations according to the invention contain 0.25 to 0.75% w/w, preferably 0.4 to 0.6% w/w, especially 0.45 to 0.55% w/w, of surfactant relative to the total weight of the solid ingredients of the formulation.

35

Preferably, the formulation according to the invention contains sorbitan monolaurate and polyoxyethylene (20) sorbitan monolaurate in a ratio of 1:7.5 to 1:8.25, such as 1:7.7 to 1:8.1

5 The formulations according to the invention are buffered to a pH of from about 5 to about 7, preferably about 6. Suitable buffers are those which are physiologically acceptable upon administration by inhalation. Such buffers include citric acid buffers and phosphate buffers, of which phosphate buffers are preferred. Particularly preferred buffers for use in the formulations of the
10 invention are monosodium phosphate dihydrate and dibasic sodium phosphate anhydrous.

The formulations according to the invention will desirably be isotonic. The formulations may be adjusted to isotonicity by addition of a suitable salt, for
15 example, sodium chloride.

Thus, in a preferred embodiment, the formulations according to the invention additionally comprise sufficient sodium chloride, or another suitable pharmaceutically acceptable salt, to provide an isotonic composition.
20

In a particularly preferred embodiment, the invention provides a formulation suitable for administration by nebulisation, which formulation consists of :

- (a) 0.5 - 2.2mg fluticasone propionate (micronised);
- 25 (b) 0.12 - 0.18mg polyoxyethylene (20) sorbitan monolaurate;
- (c) 0.015 - 0.025mg sorbitan monolaurate;
- (d) 18.5 - 19mg monosodium phosphate dihydrate;
- (e) 3.2 - 3.7mg dibasic sodium phosphate anhydrous;
- (f) 9.4 - 9.8 mg sodium chloride; and
- 30 (g) water for injection to 2.0ml.

Thus, it will be appreciated that formulations according to the preferred embodiment consist of:

- 35 (a) 0.25 - 1.1mgml⁻¹ fluticasone propionate (micronised);
- (b) 0.06 - 0.09mgml⁻¹ polyoxyethylene (20) sorbitan monolaurate;
- (c) 0.0075 - 0.0125mgml⁻¹ sorbitan monolaurate;
- (d) 9.25 - 9.5mgml⁻¹ monosodium phosphate dihydrate;

- () 1.6 - 1.85mgml⁻¹ dibasic sodium phosphat anhydrous;
- (f) 4.7 - 4.9mgml⁻¹ sodium chlorid ; and
- (g) water.

5 The formulations according to the invention form weakly flocculated suspensions on standing but, surprisingly, these suspensions have been found to be easily redispersed by mild agitation to provide suspensions with excellent delivery characteristics suitable for use in conventional nebulisers, even after prolonged storage.

10

The chemical and physical stability and the pharmaceutical acceptability of the formulations according to the invention may be determined by techniques well known to those skilled in the art. Thus, for example, the chemical stability of the components may be determined by HPLC assay, for example, after prolonged storage of the product.

15

The particle size distribution of the formulations according to the invention on nebulisation may be measured by conventional techniques, for example by cascade impaction or by the "Twin Impinger" analytical process. As used herein reference to the "Twin Impinger" assay means "Determination of the deposition of the emitted dose in pressurised inhalations using apparatus A" as defined in British Pharmacopoeia 1988, pages A204-207, Appendix XVII C. Such techniques enable the "respirable fraction" of the formulations to be calculated. As used herein reference to "respirable fraction" means the amount of active ingredient collected in the lower impingement chamber per actuation expressed as a percentage of the total amount of active ingredient delivered per actuation using the twin impinger method described above. The formulations according to the invention have been found to have a respirable fraction of 10% or more by weight of the medicament, such as 10% to 50%, for example 15% to 35%.

20
25
30

The formulations according to the invention may be prepared by conventional methods for the preparation of suspension formulations. Typically the fluticasone propionate is contacted with a small amount of surfactant solution so as to "wet" it before addition to the bulk liquid containing the remaining excipients. Constant mixing is essential to maintain a homogeneous suspension. The bulk suspension is sterilised, conveniently by means of thermal sterilisation using steam. Aliquots of the suspension are conveniently filled into

35

sterile containers, for example unit dose containers such as vials or ampoules which are suitably moulded from thermoplastics.

5 A further aspect of the present invention comprises a method of treating respiratory disorders such as, for example, asthma, which comprises administration by inhalation of an effective amount of a formulation as herein described.

10 Formulations of the present invention can, thus, be delivered by a nebuliser in which case aliquots of the suspension formulation are desirably filled into sterile containers as described above. Alternatively, the formulations of the present invention can be used as a nasal drop presentation. Thus, aliquots of the suspension formulation are desirably filled into sterile, small volume containers adapted for that delivery route.

15

The invention is further illustrated by the following non-limiting examples.

Example 1

mg

Fluticasone propionate (micronised)	0.525
Polyoxyethylene (20) sorbitan monolaurate	0.14
Sorbitan monolaurate	0.018
Monosodium phosphate dihydrate	18.80
Dibasic sodium phosphate anhydrous	3.50
Sodium chloride	9.60
Water for injection	to 2.00ml

20 It will be appreciated that the formulation prepared according to Example 1 consists of:

25 about 0.26mgml⁻¹ fluticasone propionate (micronised);
about 0.07mgml⁻¹ polyoxyethylene (20) sorbitan monolaurate;
about 0.009mgml⁻¹ sorbitan monolaurate;
about 9.4mgml⁻¹ monosodium phosphate dihydrate;
about 1.75 mgml⁻¹ dibasic sodium phosphate anhydrous;
about 4.8mgml⁻¹ sodium chloride; and
water.

The formulation prepared according to Example 1 was filled into a nebuliser. The particle size distribution on nebulisation was measured as percentage of fluticasone propionate in Stage 2 (fine particle fraction) of the Twin Impinger apparatus and as percentage of fluticasone propionate in Stages 2-7 (fine particle fraction) of the cascade impactor apparatus. Values of 18.5% and 18.2% respectively were obtained.

Example 2

	<u>mg</u>
Fluticasone propionate (micronised)	2.10
Polyoxyethylene (20) sorbitan monolaurate	0.16
Sorbitan monolaurate	0.02
Monosodium phosphate dihydrate	18.80
Dibasic sodium phosphate anhydrous	3.50
Sodium chloride	9.60
Water for injection	to 2.00ml

It will be appreciated that the formulation prepared according to Example 2 consists of:

about 1.05mgml⁻¹ fluticasone propionate (micronised);
 about 0.08mgml⁻¹ polyoxyethylene (20) sorbitan monolaurate;
 about 0.01mgml⁻¹ sorbitan monolaurate;
 about 9.4mgml⁻¹ monosodium phosphate dihydrate;
 about 1.75mgml⁻¹ dibasic sodium phosphate anhydrous;
 about 4.8mgml⁻¹ sodium chloride; and
 water.

The formulation prepared according to Example 2 was filled into a nebuliser. The particle size distribution on nebulisation was measured as for Example 1. Values of 22.1% for the Twin Impinger apparatus test and 21.6% for the cascade impactor apparatus test were obtained.

7
CLAIMS

1. A formulation suitable for nebulisation comprising:
 - (a) fluticasone propionate substantially all having a particle size of less than 12 microns;
 - (b) one or more surfactants;
 - (c) one or more buffer agents; and
 - (d) water.
2. A formulation according to claim 1, wherein the fluticasone propionate has a particle size of 1 to 6 microns.
3. A formulation according to claim 1 or claim 2, wherein the fluticasone propionate is present in an amount of 0.5 to 10% w/w based on the total weight of the solid ingredients of the formulation.
4. A formulation according to any one of claims 1 to 3, wherein the surfactant is present in an amount of 0.25% to 0.75% w/w of the total weight of the solid ingredients of the formulation.
5. A formulation according to any preceding claim, wherein the surfactants are selected from the group consisting of sorbitan trioleate, sorbitan mono-oleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan mono-oleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, glyceryl mono-oleate, polyethylene glycol 400 and glyceryl monolaurate.
6. A formulation according to claim 5, wherein the surfactants are sorbitan monolaurate and polyoxyethylene (20) sorbitan monolaurate.

7. A formulation according to claim 6, wherein the sorbitan monolaurate and polyoxyethylene (20) sorbitan monolaurate are present in a ratio of 1:7.5 to 1:8.25.
8. A formulation according to any preceding claim which is buffered to a pH of from about 5 to about 7.
9. A formulation according to any preceding claim which is isotonic.
10. A formulation according to any preceding claim, comprising:
 - (a) 0.25 - 1.1mgml⁻¹ fluticasone propionate (micronised);
 - (b) 0.06 - 0.09mgml⁻¹ polyoxyethylene (20) sorbitan monolaurate;
 - (c) 0.0075 - 0.0125mgml⁻¹ sorbitan monolaurate;
 - (d) 9.25 - 9.5mgml⁻¹ monosodium phosphate dihydrate;
 - (e) 1.6 - 1.85mgml⁻¹ dibasic sodium phosphate anhydrous;
 - (f) 4.7 - 4.9mgml⁻¹ sodium chloride; and
 - (g) water.
11. A formulation according to claim 10 comprising:
 - (a) about 0.26mgml⁻¹ fluticasone propionate (micronised);
 - (b) about 0.07mgml⁻¹ polyoxyethylene (20) sorbitan monolaurate;
 - (c) about 0.009mgml⁻¹ sorbitan monolaurate;
 - (d) about 9.4mgml⁻¹ monosodium phosphate dihydrate;
 - (e) about 1.75 mgml⁻¹ dibasic sodium phosphate anhydrous;
 - (f) about 4.8mgml⁻¹ sodium chloride; and
 - (g) water.
12. A formulation according to claim 10 comprising:
 - (a) about 1.05mgml⁻¹ fluticasone propionate (micronised);
 - (b) about 0.08mgml⁻¹ polyoxyethylene (20) sorbitan monolaurate;
 - (c) about 0.01mgml⁻¹ sorbitan monolaurate;
 - (d) about 9.4mgml⁻¹ monosodium phosphate dihydrate;
 - (e) about 1.75mgml⁻¹ dibasic sodium phosphate anhydrous;
 - (f) about 4.8mgml⁻¹ sodium chloride; and
 - (g) water.

13. A method of preparing a formulation according to any preceding claim comprising contacting the fluticasone propionate with a solution of surfactant and mixing the resultant drug/surfactant solution with the other components of the formulation.
14. A container comprising a formulation according to any one of claims 1 to 12.
15. Use of a formulation according to any one of claims 1 to 12 in a nebuliser to produce a plurality of droplets of said formulation, said droplets being suitable for inhalation.
16. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of a formulation comprising:
 - (a) fluticasone propionate substantially all having a particle size of less than 12 microns;
 - (b) one or more surfactants;
 - (c) one or more buffer agents; and
 - (d) water.

INTERNATIONAL SEARCH REPORT

 Internat. Application No
 PCT/EP 95/01913

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K9/00 A61K31/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DRUG INVESTIGATION, vol.8, no.3, 1994 pages 127 - 133 AINGE, G.; ET AL. 'Lack of deleterious effects of corticosteroid sprays containing benzalkonium chloride on nasal ciliated epithelium' see the whole document ---	1-16
A	RHINOLOGY, vol.11, 1991 pages 37 - 43 SCADDING, G.K.; ET AL. 'clinical and physiological effects of fluticasone propionate aqueous nasal spray in the treatment of perennial rhinitis' see the whole document --- -/--	1-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

28 September 1995

Date of mailing of the international search report

10.10.95

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Internat. Application No.
PCT/EP 95/01913

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO,A,93 17665 (SIEVERS, ROBERT E.; ET AL.) 16 September 1993 see claims 1,8,11 see page 7, line 7 - line 18 see page 8, line 3 - line 6 -----</p>	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internet Application No

PCT/EP 95/01913

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9317665	16-09-93	US-A- 5301664	12-04-94
		CA-A- 2131393	16-09-93
		EP-A- 0627910	14-12-94
